22q11.2 Deletion Syndrome

Synonyms: DiGeorge syndrome, hypoplasia of the thymus and parathyroids, third and fourth pharyngeal pouch syndrome, velo-cardio-facial syndrome, Shprintzen syndrome

Introduction

In 1965 DiGeorge described a patient with hypoparathyroidism and cellular immune deficiency secondary to thymic hypoplasia. Soon the pattern of malformation included in this syndrome expanded to include other defects of third and fourth branchial arches as well as dysmorphic facial features. In 1978 Shprintzen reported a group of children with cleft palate or velopharyngeal incompetence, cardiac defects and a prominent nose (velo-cardio-facial syndrome). It was subsequently determined that individuals with velo-cardio-facial syndrome and the majority of those with the condition described by DiGeorge have a deletion of chromosome 22q11.2. It is now understood that both these disorders represent different manifestations of the same genetic defect.[1]

Genetics and genetic counselling

The 22q11.2 deletion is a 1.5 to 3 megabase deletion on the long (q) arm of chromosome 22. The deletion contains TBX1, the major candidate gene, and other genes controlling the 3rd and 4th pharyngeal arches, brain and skeletal development. Haploinsufficiency results in the development of the syndrome phenotype.

Inheritance is autosomal dominant but most cases have a de novo 22q deletion.[2] Fewer than 10% of the patients show familial transmission of 22q11.2 deletion. Penetrance is 100% with highly variable expression.[3] Variable expression is evident even in cases with the same deletion. An unaffected parent may carry the deletion in their egg or sperm (germline mosaicism) with a recurrence risk of 1% in subsequent pregnancies.

With rapid advances in molecular cytogenetics, the investigation of choice is a standard karyotype to exclude major rearrangements and fluorescence in situ hybridisation (FISH) using probes from within the deletion segment. Parents should be screened for career status.[4] While genetic diagnosis using FISH can be confirmed in 95% of cases, the remaining 5% with atypical deletions require more advanced techniques, including chromosomal micro-array analysis.[5]

Because subjects with 22q11.2 deletion have a 50% risk of transmitting the deletion, they should be offered genetic counselling and FISH for prenatal detection (at 10-12 weeks of gestation) by chorionic villus sampling.

Epidemiology

It occurs in approximately 1 in 4,000 births and the incidence is increasing because of affected parents bearing their own affected children.[6]

The exact prevalence is difficult to estimate, as the number of individuals diagnosed depends on the experience and awareness of the syndrome among specialists who encounter these children and also the severity of phenotype as evidenced by a Swedish demographic study.[7] The prevalence was estimated as 13.2 per 100,000 in western Sweden but much higher, at 23.3 per 100,000, in Gothenburg where a specialist multidisciplinary team was based.

Presentation

The phenotypic spectrum is highly variable with more than 190 features reported, including congenital heart disease, velopharyngeal insufficiency and cleft palate, immune disorders, feeding difficulties, and hypocalcaemia secondary to hypoparathyroidism.[8] Typically, babies are born with a conotruncal cardiac abnormality and mild-to-moderate immune deficiency. Developmental delay, facial dysmorphism, palatal dysfunction and feeding difficulties are seen in most infants with this syndrome.

Possible clinical findings with their frequency are best summarised in the table based on data taken from the Kobrynski et al review published in Lancet.[9] Some of the findings are then explored in greater detail.
Clinical findings in patients with 22q11.2 deletion syndrome

<table>
<thead>
<tr>
<th>Clinical findings</th>
<th>Frequency</th>
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<tbody>
<tr>
<td>Cardiac anomalies</td>
<td>49-83%</td>
</tr>
<tr>
<td>Hypocalcaemia</td>
<td>17-60%</td>
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<tr>
<td>Growth hormone deficiency</td>
<td>4%</td>
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<tr>
<td>Palatal anomalies</td>
<td>69-100%</td>
</tr>
<tr>
<td>Renal anomalies</td>
<td>36-37%</td>
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<tr>
<td>Ophthalmological abnormalities</td>
<td>7-70%</td>
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<tr>
<td>Neurological abnormalities</td>
<td>8%</td>
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<tr>
<td>Cervical spine anomalies</td>
<td>40-50%</td>
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<tr>
<td>Lower limb anomalies</td>
<td>15%</td>
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<tr>
<td>Speech delay</td>
<td>79-84%</td>
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<tr>
<td>Developmental delay in infancy</td>
<td>75%</td>
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<tr>
<td>Developmental delay in childhood</td>
<td>45%</td>
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<tr>
<td>Behavioural or psychiatric problems</td>
<td>9-50%</td>
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Cardiac
Cardiac malformations are seen in approximately 75% of patients with 22q11.2 deletion syndrome. They particularly affect the outflow tract. They include Fallot's tetralogy, type B interrupted aortic arch, truncus arteriosus, right aortic arch and aberrant right subclavian artery. Cases presenting later tend to have a milder spectrum of cardiac defect with ventricular septal defect being common.

Hypocalcaemia
Hypocalcaemia is usually due to hypoparathyroidism and is variable in duration, from being restricted to the neonatal period to lasting for months to years. However, it is not usually lifelong. It may be asymptomatic (biochemical) or present as tetany, seizures or stridor. It may also be precipitated by stress of surgery or increased needs of puberty or pregnancy.

Immune deficiency
Immune deficiency is common and usually mild. A low number of T cells is seen in 75-80% of infants with 22q11.2 deletion syndrome and pose no additional risk at surgery. Thymus may be absent. Less than 1% of the patients have no T cells and need protection from infection and blood products. T-cell deficiency improves spontaneously and resolves in most children by 2 years of age. Reduced levels of IgA and IgM in older children occur more frequently than in the general population. There is an increased tendency to have infections, especially of the respiratory tract.

Feeding and growth
Feeding and swallowing difficulties are common in infancy because of poor co-ordination of the pharyngeal muscles, the tongue and the oesophageal muscles. Gastro-oesophageal reflux is also common and dysphagia may cause silent aspiration and pneumonia. Patients with cardiac defects may have shortness of breath, causing difficulty in feeding and faltering growth.

Facies
The facial dysmorphism is typically mild but fairly typical. These include hypertelorism, hooded eyelids, tubular nose, broad nose tip, small mouth and mild ear abnormalities.

Hearing and speech
Hearing is important for language development. About 10% of patients with 22q11.2 deletion syndrome have sensorineural hearing loss, and about 45% conductive loss.

75% of affected individuals have hypernasal speech and a high percentage has severe articulation impairment. DiGeorge's syndrome is the most frequent clefting syndrome and may be responsible for up to 8% of children with palatal clefts seen in some hospitals.
Speech difficulties include defects in phonation, in language acquisition and in comprehension. Expressive language and speech skills are usually more delayed than receptive skills and worse than would be expected on the basis of cognitive development. Social language skills are even more delayed and this pattern of skill weakness is considered typical of 22q11.2 deletion syndrome. Ultimately, most patients learn to speak and communicate effectively.

Renal problems
Renal agenesis, duplication of kidneys, dysplastic kidneys, duplicated ureters and other minor malformations are seen in about a third of patients. Nephrocalcinosis can also develop because of excessive calcium replacement for hypocalcaemia.

Behavioural and psychiatric problems
The behavioural issues related to 22q11.2 deletion syndrome include attention deficit hyperactivity disorder, poor social interaction skills, and impulsivity. More than 40% of patients meet the criteria for either autistic spectrum disorder, attention deficit/hyperactivity disorder, or both. Bipolar disorder, autistic spectrum disorder and schizophrenia or schizoaffective disorder are reported in 10-30% of teenagers and adults. A variety of psychiatric disorders has been described in a small proportion of adult cases, including paranoid schizophrenia and major depressive illness. The risk for severe psychiatric illness is 25 times higher than in the general population.

Developmental delay and learning difficulties
The mean IQ in children with 22q11.2 deletion syndrome is around 70, indicating a range from normal to moderately disabled. About 30% lie in the normal range of IQ between 80-100 and fewer than 20% have moderate-to-severe learning difficulties. Not all cognitive skills are affected and most patients have reasonable skills in areas of comprehension and social rules. The weakest cognitive skills tend to be visuo-perceptual ability and planning. Ability to grasp abstract concepts, especially mathematics, is weak; however, memory (and therefore rote learning) is alright.

Musculoskeletal disorders
Hypotonia and ligamentous laxity are common along with frequent symmetric leg pains. Inco-ordination, clumsy gait and clumsy hand skills are common and the incidence of rheumatoid arthritis and patellar dislocation is higher than in the general population. Congenital club foot is also common.

The prevalence of scoliosis is 3-8 times that of the general population. Hemivertebrae and other skeletal abnormalities can also occur. Radiological abnormalities of the cervical spine are common, although evidence of cord compression is rare and cervical spine X-ray findings do not seem to be predictive of subsequent dislocation or subluxation of the atlanto-axial joint.

Differential diagnosis
- CHARGE (coloboma (eye), heart anomaly, atresia (choanal), retardation (developmental and growth), genital anomaly, ear anomaly) syndrome.
Investigation and management

Guidelines for best practice management of 22q11.2 deletion syndrome in the UK have been developed by a national group of professionals based on literature review and consensus. These recommendations, which are based on various levels of evidence and include some expert opinion-based good practice points, are summarised in the table below, followed by a more detailed discussion of some aspects of management.

<table>
<thead>
<tr>
<th>Recommendations for investigation, management and referral [10]</th>
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<tbody>
<tr>
<td><strong>Investigations at diagnosis</strong></td>
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<td>- FBC, including differential white cell count, lymphocyte phenotyping, immunoglobulins G, A and M. Lymphocyte proliferation testing if readily available and T-cell count is low; post-immunisation tetanus or Hib antibodies.</td>
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<td>- Serum calcium, thyroid function.</td>
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<td>- Cardiological examination, echocardiogram and electrocardiogram.</td>
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<td>- Parental 22q11.2 status, and that of siblings if a parent is affected.</td>
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<td>- Renal ultrasound scan, looking for a single kidney, cysts, or dilated collecting system.</td>
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<td><strong>Essential initial actions</strong></td>
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<td>- Irradiated cytomegalovirus-negative blood products if immune status is unknown or severely affected. Urgent specialist referral if T lymphocytes appear virtually absent or very low.</td>
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<tr>
<td>- Vaccination: primary vaccination should be given promptly, including mumps, measles and rubella (MMR), even if the CD4 count is low. Chickenpox vaccination is not given with a CD4 count below 200/mL, as in human immunodeficiency virus. Avoid BCG and consult an immunologist if circumstances require this.</td>
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<tr>
<td><strong>Specific medical examinations</strong></td>
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<td>- Genetics: at diagnosis, and repeated when the family and emerging adult have a need.</td>
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<td>- Special senses: hearing test and eye examination at diagnosis. Orthoptic and refractive examination at 3 years and ophthalmic examination as clinically indicated.</td>
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<tr>
<td>- Musculoskeletal system:</td>
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<td>- Scoliosis examination at diagnosis and between 10 and 12 years, in the earlier part of the adolescent growth spurt.</td>
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<td>- Locomotor system:</td>
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<td>- Examination for limb pain, stiffness, and swelling; arthritis can present as delayed development in young children. Depending on clinical findings, appropriate investigations include inflammatory markers, autoimmune serology, and ultrasound.</td>
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<tr>
<td>- Height and weight: monitor frequently up to the age of 2 and annually thereafter. Slowing of growth warrants full assessment, including screening for thyroid and growth hormone deficiency.</td>
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<td>- Autoimmune disorders, if clinically indicated: autoantibodies, including direct antiglobulin test and thyroid antibodies.</td>
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As there is a wide spectrum of phenotypes, management needs to be tailored to the individual.

- Cardiac defects are the usual focus of clinical management, unless very mild. Treatment is individualised according to the cardiac defect. A cardiology opinion, ECG and echocardiogram are indicated at the time of genetic diagnosis if not already done. If the first assessment is normal, no further routine review is needed. Surgery does not carry a worse prognosis. [12] Treatment is guided by individual cardiac lesion.
- Hypocalcaemia should be screened for by checking calcium levels three-monthly in infancy and then annually. Low calcium and high phosphate levels should prompt further testing of parathyroid hormone and vitamin D levels. Calcium supplements and 1,25-calciferol are effective treatments for hypocalcaemia but should be used with careful monitoring in individuals with associated renal anomalies.
- All patients should have baseline immunological testing and annual blood count. About 1% of patients have severe immune deficiency with thymic aplasia and absent T cells. These should be referred urgently to a supra-regional centre for assessment and possible thymic transplantation. Immunoglobulin replacement along with prophylactic antiviral, antifungal and anti-pneumocystis medications need to be commenced. Recipient survival of 70% has been reported in patients with athymia undergoing thymic transplantation. [13]
- Any affected child undergoing major surgery should have a supply of irradiated blood to avoid graft-versus-host disease (until immunocompetence has been demonstrated).
- Cleft palates may be submucous. In particular, they should be sought if feeding difficulties are encountered in the neonatal period. The child should be referred to the local cleft lip and palate team.
- Gastro-oesophageal reflux needs to be managed appropriately with feed thickeners and anti-reflux medication.
- Nasogastric tube feeding and occasionally gastrostomy may be needed to deal with feeding issues.
- Management shifts to cognitive, behavioural, and learning disorders during school years. Speech therapy and additional educational assistance may be needed.
- In late adolescence and adult years the potential for psychiatric disorders (including psychosis) requires vigilance.

Prognosis [8]

Although cardiac problems improve after surgery in the majority of patients, cardiac malformations still remain the main cause of death in the first year of life. The prognosis for the resolution of speech problems is good with appropriate interventions, and the incidence of infections decreases over time. The large majority of babies have successful corrections of their heart disease and will have normal lifespans.
Further reading & references

- Consensus Document on 22q11 Deletion Syndrome (22q11.2DS); Max Appeal
- Cutler-Landsman D; Educating Children with Velo-Cardio-Facial Syndrome (also Known as 22q11.2 Deletion Syndrome and DiGeorge Syndrome) 2nd edition; Plural Publishing, 2012
- Max Appeal
- Velo-Cardio-Facial Syndrome (VCFS) Educational Foundation

1. 22Q11.2 Microdeletion Syndrome (Velo-Cardio-Facial Syndrome, DiGeorge Syndrome, Shprintzen Syndrome); Smith’s Recognizable Patterns of Human Malformation
3. DiGeorge Syndrome, DGS; Online Mendelian Inheritance in Man (OMIM)

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